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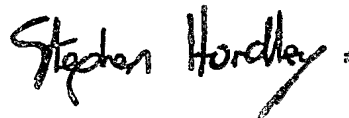
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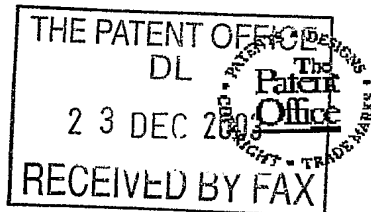
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4. Title of the invention

ROMP POLYMER SYNTHESIS

5. Name of your agent (if you have one)

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to which all correspondence should be sent
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Description

21

Claim(s)

5

Abstract

1

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Priority documents

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Statement of inventorship and right to grant of a patent (Patents Form 7/77)

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11. I/We request the grant of a patent on the basis of this application.

Signature(s) ROLLINS, Anthony, John

A. J. Rollins

Date 23 December 2003

12. Name, daytime telephone number and e-mail address, if any, of person to contact in the United Kingdom

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ROMP Polymer Synthesis

Technical Field of the Invention

The present invention relates to the field of solid-phase radiochemistry. More specifically, the present invention relates to solid phase radiochemistry carried out on
5 the internal surfaces of a device wherein said internal surfaces are coated with a ring-opening metathesis polymerisation (ROMP) polymer.

Description of Related Art

Ring-opening metathesis polymerisation (ROMP) is a variant of the olefin metathesis reaction. One of the main advantages of ROMP polymers is that in principle every
10 monomer unit carries a functional group and should give much higher loading than some other polymers. ROMP is known for the production of functionalised polymers for organic synthesis (Barrett *et al* Chemical Reviews 2002 102 pp 3301-24). A number of other chemical applications have been reported, e.g. chromatography, solid-phase extraction, construction of synthetic libraries and purification, all of which are discussed
15 by Barrett *et al*.

The application of ROMP polymers to the surfaces of devices has also been reported. In WO 03/093406 ROMP polymers are suggested as a means to alter the surfaces of a miniaturised bioreactor to render them more biocompatible, i.e. that the cell viability and proliferation and/or other biological components produced by the cells are not adversely
20 affected by contact with the surface.

In US 2002/0122747 microdevices are fabricated with ROMP polymers in order to enable metallization of the surfaces. The side chains of the ROMP polymer are selected such that they bind to the desired metal. The integration of components such as electrodes, heaters and valves is therefore permitted, rendering the microdevice
25 more functional.

Summary of the Invention

The present invention involves the application of ROMP polymers to the internal surfaces of a device for the purpose of carrying out a solid-phase radiochemical process within the device. An additional embodiment of the invention is an automated synthesis

system comprising a number of devices of the invention in order that a series of processes can be carried out in direct sequence. In a preferred embodiment, the present invention is a microfabricated device.

Detailed Description of the Invention

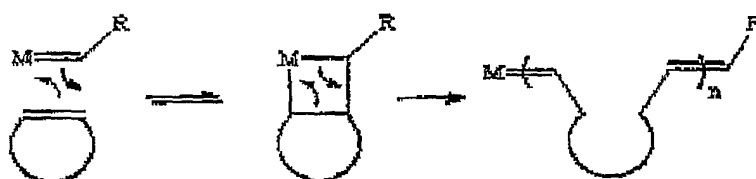
5 In a first aspect, the present invention relates to a device adapted to carry out a solid-phase radiochemical process characterised in that the solid-phase radiochemical process is carried out on the internal surfaces of said device wherein said internal surfaces are coated with a Ring Opening Metathesis Polymerisation (ROMP) polymer.

10 A "device adapted to carry out a solid-phase radiochemical process" may comprise one or more components, e.g. a laboratory vessel made from glass, glassy carbon or a metal such as stainless steel, a well of a microplate, polymer tubing or a microfabricated device. Due to the radioactive nature of the process, such devices are provided with shielding to protect the operator from radioactive contamination. Such shielding suitably takes the form of a lead barrier or box around the device. Furthermore, the devices
15 according to the invention are suitably connected to or incorporate a means of radiochemical detection, for example a positron detector or HPLC system fitted with a radioactivity detector.

The "internal surface" of the device is taken to mean the surface that comes into contact with the reactants introduced into the device. Therefore, when the internal surface is
20 coated with a ROMP polymer, the reactants come into contact with the side chains of the ROMP polymer. The side chains themselves participate in the chemical process, and because they can be virtually any organic substituent the polymer can be tailored to be suitable for carrying out a specific chemical process.

"ROMP polymer" is defined in the present invention as a polymer obtained by the
25 ROMP reaction. The ROMP reaction uses strained cyclic olefins to produce stereoregular and monodisperse polymers and co-polymers. The mechanism of ROMP reaction involves an alkylidene catalyst and is identical to the mechanism of olefin synthesis except that, as the reaction involves a cyclic olefin, the new olefin that is generated stays attached to the catalyst as part of a growing polymer chain as
30 illustrated below:

3



Wherein M is a metal selected from molybdenum and ruthenium and R is an organic substituent.

- 5 The driving force of the ROMP reaction is the relief of the strain on the ring such that the second step in the reaction above is essentially irreversible. Strained cyclic olefins such as those illustrated below have sufficient ring strain to make the reaction possible:



A preferred ROMP polymer of the present invention is of Formula I:



10

wherein:

X is either a C₁₋₆ hydrocarbon chain or a C₄₋₆ alicyclic group;

- 15 R¹ is selected from hydrogen, hydroxyl, halogen, nitro, cyano, -SH, -N=C=O, C₁₋₂₀ alkyl, C₄₋₁₂ aryl, C₃₋₂₀ alkylaryl, C₂₋₂₀ acyl, C₂₋₂₀ functionalised acyl, C₁₋₂₀ formyl, C₁₋₂₀ functionalised formyl, C₁₋₂₀ alkoxy, C₁₋₂₀ functionalised alkoxy, C₁₋₂₀ amino, C₁₋₂₀ functionalised amino, C₃₋₁₈ trialkylammonium, C₃₋₁₈ trialkylammonium with bound fluoride ion, C₁₋₂₀ imino, C₁₋₂₀ functionalised imino, C₁₋₂₀ amido, C₁₋₂₀ functionalised amido, C₁₋₂₀ nitroalkyl, C₁₋₂₀ functionalised nitroalkyl, C₁₋₂₀ carboxyl, C₁₋₂₀ functionalised carboxyl, carbonate, C₂₋₂₀ carboalkoxy or C₂₋₂₀

functionalised carboalkoxy or R^1 optionally further comprises a radiotracer precursor, a catalyst or an enzyme;

$-(L)_y-$ is linker group wherein each L is independently $-CY_2-$, $-CY=CY-$, $-C\equiv C-$, $-CY_2CO_2-$, $-CO_2CY_2-$, $-NYCO-$, $-CONY-$, $-NY(C=O)NY-$, $-NY(C=S)NY-$, $-SO_2NY-$, $-NYSO_2-$, $-CY_2OCY_2-$, $-CY_2SCY_2-$, $-CY_2NYCY_2-$, a C_{4-8} cycloheteroalkylene group, a C_{4-8} cycloalkylene group, a C_{5-12} arylene group, or a C_{3-12} heteroarylene group, or an amino acid, wherein Y is independently chosen from H, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxyalkyl or C_{1-4} hydroxyalkyl and y is an integer of value 0 to 10; L is optionally further substituted with one or more R^2 groups where R^2 is selected from hydrogen, hydroxyl, halogen, nitro, cyano, $-SH$, $-N=C=O$, C_{1-20} alkyl, C_{4-12} aryl, C_{3-20} alkylaryl, C_{2-20} acyl, C_{2-20} functionalised acyl, C_{1-20} formyl, C_{1-20} functionalised formyl, C_{1-20} alkoxy, C_{1-20} functionalised alkoxy, C_{1-20} amino, C_{1-20} functionalised amino, C_{3-18} trialkylammonium, C_{1-20} imino, C_{1-20} functionalised imino, C_{1-20} amido, C_{1-20} functionalised amido, C_{1-20} nitroalkyl, C_{1-20} functionalised nitroalkyl, C_{1-20} carboxyl, C_{1-20} functionalised carboxyl, carbonate, C_{2-20} carboalkoxy or C_{2-20} functionalised carboalkoxy; and,

n = number of polymer units.

"Alkyl" used either alone or as part of another group is defined herein as any straight, branched or cyclic, saturated or unsaturated C_xH_{2x+1} group.

"Aryl" used either alone or as part of another group is defined herein as any C_{6-14} molecular fragment or group which is derived from a monocyclic or polycyclic aromatic hydrocarbon. Suitable aryl groups of the invention include, but are not limited to, haloaryl, alkylaryl, arylcarbonyl, phenylazo, arylamino, arylthio, toluene, benzoic acid, phenol, arylsulfinyl, arylsulfonyl, arylsulfonamido, benzothiophene, naphthalene, quinoline, isoquinoline, pyridine, pyrimidine, and pyrazine.

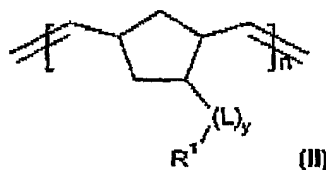
R^1 is preferably halogen, C_{1-20} alkyl, C_{4-12} aryl, C_{3-20} alkylaryl, C_{1-20} amine, C_{1-20} functionalised amine, C_{1-20} carboxylic acid, C_{1-20} functionalised carboxylic acid or a group comprising an enzyme.

5

R^1 is most preferably trialkylammonium; trialkylammonium with bound ^{18}F -fluoride ion; C_{1-20} alkyl; $-\text{N}=\text{C}=\text{O}$; or $-\text{SH}$, or comprises an enzyme or a catalyst.

It is additionally suitable for more than one particular R^1 group to be present in the ROMP polymer of the invention. This is achieved by the inclusion of more than one
 5 type of monomer in the reaction mixture and enables the swelling properties of the resultant polymer to be tailored as well as the production of a dual- or multi-capacity device.

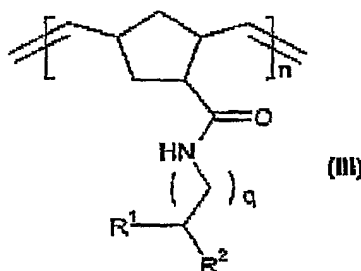
A most preferred ROMP polymer of the present invention is of Formula II:



10 wherein:

$-(\text{L})_y$, R^1 and n are as defined in claim 2 for Formula I.

An especially preferred ROMP polymer of the present invention is of Formula III:



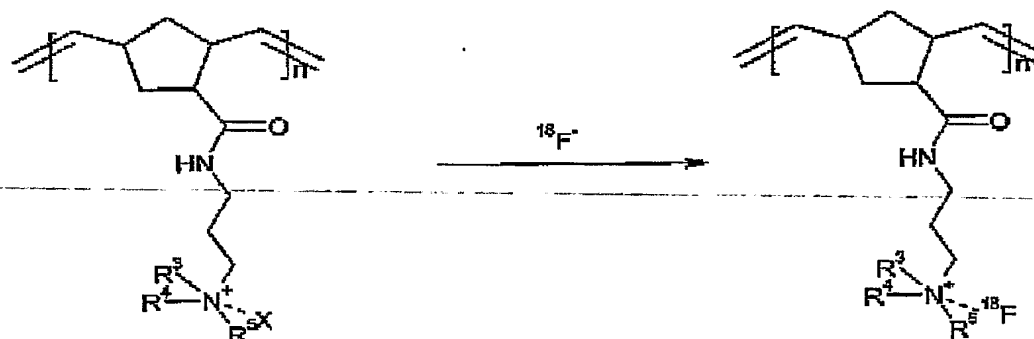
wherein:

15 R^1 and n are as defined in claim 2 for Formula I;

R^2 is an optional group as defined in claim 2 for $-(\text{L})_y$ of Formula I; and,

$q = 1-4$.

A most especially preferred ROMP polymer of the present invention is of Formula III wherein R^1 is trialkylammonium, R^2 is absent, $q = 3$ and $n =$ number of polymer units. When R^1 of Formula III is trialkylammonium, the device is particularly suitable for the recovery of ^{18}F -fluoride ion from ^{18}O -enriched water containing ^{18}F -fluoride ion, or natural water containing ^{18}F -fluoride ion, as shown in the scheme below:



wherein R^3 - R^5 are C_{1-8} alkyl groups and X is a non-nucleophilic anion, e.g. carbonate, bicarbonate or oxalate.

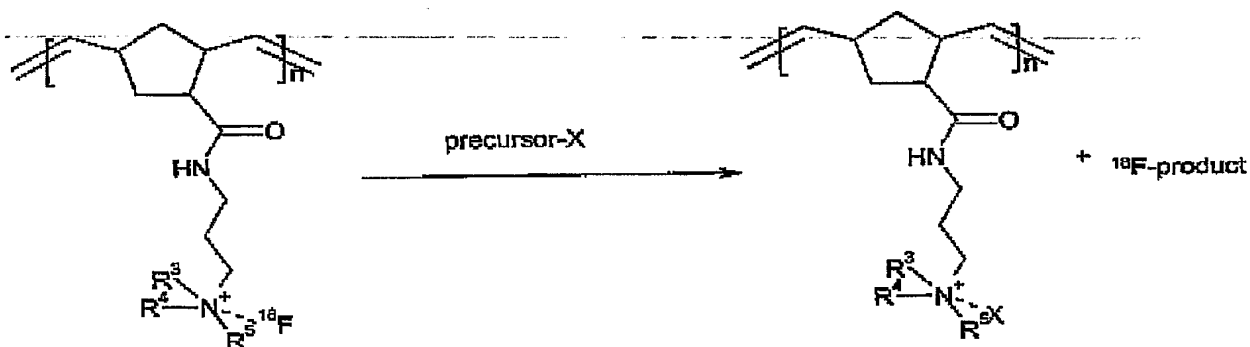
R^1 of Formula III then becomes trialkylammonium with bound ^{18}F -fluoride ion, which renders the device particularly suitable for carrying out *in situ* radiofluoridations.

Preferably, the *in situ* radiofluoridation forms a step in the synthesis of an ^{18}F -labelled radiotracer. The term "radiotracer" as used herein includes carrier-added and no carrier-added radiolabelled compounds, and in particular includes radioligands (compounds radiolabelled at high specific activity).

The skilled person will appreciate that use of other suitable R groups will enable immobilisation of other radiolabels of interest and their subsequent use for *in situ* radiolabelling reactions. Examples of other suitable radiotracer labels that can be immobilised for *in situ* radiolabelling reactions include: other non-metal positron emitters such as ^{11}C , ^{13}N , ^{15}O , ^{17}F , ^{75}Br , ^{76}Br or ^{124}I ; positron-emitting radioactive metals such as ^{64}Cu , ^{48}V , ^{52}Fe , ^{55}Co , $^{94\text{m}}\text{Tc}$ or ^{68}Ga ; gamma-emitting radioactive halogens such as ^{123}I , ^{125}I , ^{131}I or ^{77}Br ; and gamma-emitting radioactive metal ions such as $^{99\text{m}}\text{Tc}$.

Specific examples of ^{18}F -labelled radiotracers which may be prepared using the ROMP polymer of Formula III where R^1 is trialkylammonium with bound ^{18}F -fluoride ion, R^2 is

absent, $q = 3$ and $n =$ number of polymer units, include: 2- ^{18}F fluorodeoxyglucose (2- ^{18}F -FDG); L-6- ^{18}F fluoro-DOPA; 3'-deoxy-3'-fluorothymidine (FLT); 2-(1,1-dicyanopropen-2-yl)-6-(2- ^{18}F fluoroethyl)-methylamino)-naphthalene (^{18}F FDDNP); 5- ^{18}F fluorouracil; 5- ^{18}F fluorocytosine; and, ^{18}F -1-amino-3-fluorocyclobutane-1-carboxylic acid (^{18}F -FACBC). In each case, an unlabelled precursor compound of the ^{18}F -labelled radiotracer is introduced into the device. ^{18}F becomes incorporated into the precursor compound via nucleophilic substitution to form the ^{18}F -labelled radiotracer as illustrated below:

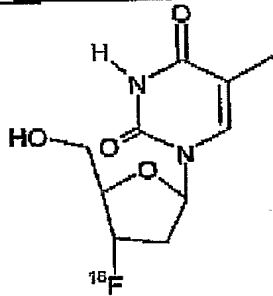
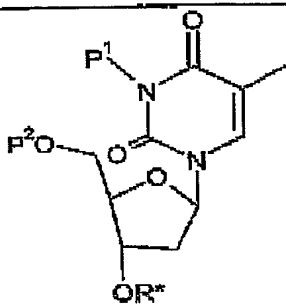
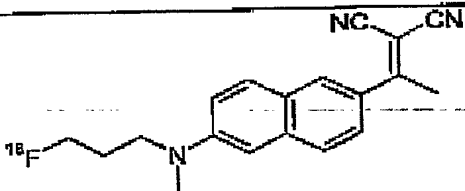
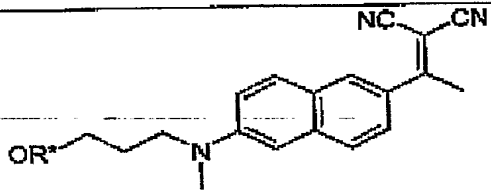
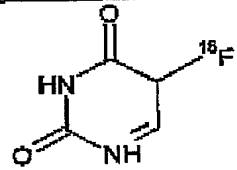
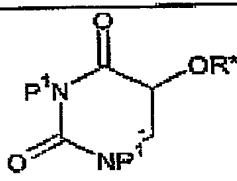
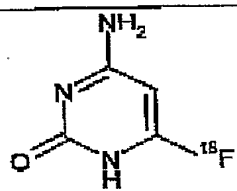
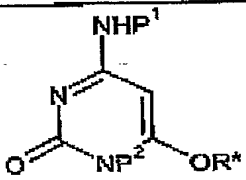
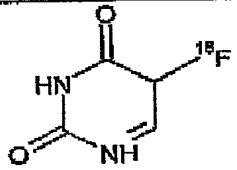
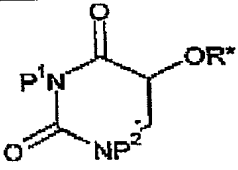


wherein R³-R⁵ are C₁₋₆ alkyl groups and X is a non-nucleophilic anion, e.g. carbonate, bicarbonate or oxalate.

The structures of various ^{18}F -labelled radiotracers and suitable precursors for their synthesis are given in Table I:

Table I

^{18}F -labelled radiotracer	Precursor
2- ^{18}F FDG	
^{18}F FLT	

	
[¹⁸F]FDDNP	
	
5[¹⁸F]fluorouracil	
	
5[¹⁸F]fluorocytosine	
	
[¹⁸F]-FACBC	
	

In Table I above, R* is triflate or nonaflate and P¹-P⁴ are each a protecting group.

Suitable protection may be achieved using standard methods of protecting group

chemistry. After the fluoridation is complete, any protecting groups may be removed by

simple procedures which are also standard in the art. Suitable protection and

5 deprotection methodologies may be found, for example, in *Protecting Groups in Organic*

Synthesis, Theodora W. Greene and Peter G. M. Wuts, published by John Wiley & Sons Inc.

It will be appreciated by those skilled in the art that production of radiotracers may also be suitably carried out on a device wherein R^1 of Formulae I-III comprises the radiotracer precursor. Radioabelling is achieved by introducing the radiolabel into the device, such that the radiolabelled product becomes detached from the polymer once radiolabelling has taken place successfully.

When R^1 of any of Formulas I to III is a C_{1-20} alkyl group, the device is particularly suitable for performing chromatographic separations. A preferred side chain is a C_{18} hydrocarbon as this is the most commonly used side chain for reverse-phase chromatography, which is a chromatographic technique in which analytes bind non specifically through hydrophobic interaction. The bound analytes can be eluted by gradient elution using a solution of ever increasing or decreasing polarity.

When R^1 of any of Formulas I to III is a group comprising an enzyme, the device is particularly suitable for carrying out enzymatic reactions. With the enzyme immobilised on the ROMP polymer there is no necessity to have a separate step in the process for the removal of enzyme from the reaction mixture. An example reaction is the conversion of ^{14}C -thymine to ^{14}C -thymidine wherein thymidine phosphorylase is immobilised into the ROMP polymer. It will be appreciated that many other enzymatic reactions can be carried out in this way.

When R^1 of any of Formulas I to III is $-SH$, the device is particularly suitable as a scavenger, e.g. for taking up mercury ions from a solution.

A particularly preferred embodiment of the device of the present invention is a microfabricated device. In microfabricated devices, predetermined networks of microchannels or capillaries, typically $10-300\mu m$, more typically $50-300\mu m$ in diameter, are etched or otherwise machined on the surface of a substrate, suitably made of glass or silicon. Alternatively, the microchannels may be created using polydimethylsiloxane, which may be poured over a master (usually glass), allowed to cure and then peeled off, or are fabricated by injection moulding, hot embossing, casting, lithography, or machining. These channels may be sealed through bonding of a cover plate, suitably

made from a metal (for example, gold, platinum or silver) or, more commonly, glass, creating a contained network capable of manipulating picolitre to microlitre volumes of liquid or gas. The sealing method used depends on the materials selected and may be selected from thermal bonding (for glass chips), anodic bonding (for silicon chips), and for polymer chips the sealing method may be selected from clamping, gluing, application of heat and pressure, and natural adhesion. Nanolitre and picolitre volumes may be used for analytical aspects but the devices can handle flows of up to hundreds of microlitres per minute. This could be increased further, for example, by stacking multiple devices. These devices are designed to be used either with micro syringe pumps (available from Kloehe Limited, Las Vegas, USA) or under electroosmotic flow. Fused silica capillaries can be used for interfacing with reagents or reagent sources and analytical systems (such as ultraviolet (UV), capillary electrophoresis (CE), capillary electrochromatography (CEC), electrochemical, refractive index, and radioactivity detectors).

15 A second aspect of the present invention is a method for the production of a microfabricated device of the invention comprising:

- (i) creating a defined network of microchannels within said device;
- (ii) heating the device to a temperature of between 80°C and 140°C; and,
- (iii) passing a solution of monomer, crosslinker and catalyst through the microchannels while concurrently introducing a flow of nitrogen through the microchannels such that ROMP polymer is deposited on walls and indentations of the microchannels.

Step (i) above may comprise the following steps:

- (a) providing a suitable substrate;
- (b) marking a specific pattern onto the surface of said substrate;
- (c) etching the pattern into the surface of said substrate; and
- (d) attaching a cover to the etched surface of step (c) thereby forming channels.

Alternatively, step (i) can comprise the use of a polymer in a process selected from injection moulding, hot embossing, casting, lithography or machining.

In a third aspect of the present invention, it is envisaged that a number of such microfabricated devices could be fluidly interconnected to form an automated synthesis system. A series of solid-phase radiochemical processes can be carried out within the system, e.g. a mixing and reaction device followed by an analysis device and finally a separation device. Such an automated synthesis system would enable the complete automation of a series of solid-phase radiochemical processes. This is desirable as it means (i) minimum user contact with radioactive reactants and (ii) the process takes as little time as possible thereby achieving a high specific activity product.

In a fourth aspect, the present invention relates to the use of the device of the invention for:

- (i) recovery of radioisotopes;
- (ii) radiochemical synthesis; or
- (iii) radiochemical purification.

In a fifth aspect, the present invention relates to a process for labelling the precursor of a radiotracer with a radiolabel characterised in that the radiolabel is provided bound to a ROMP polymer. Suitable radiolabels are positron emitters such as ^{18}F and ^{11}C ; gamma-emitting radioactive halogens such as radioiodine; and, radioactive metal ions such as $^{99\text{m}}\text{Tc}$.

Brief Description of the Examples

Example 1 describes the synthesis of ROMP monomer suitable for preparing a ROMP polymer for fluoride (ion-exchange) extraction.

Example 2 describes the synthesis of the cross-linker used in the reaction to polymerise the monomer prepared in Example 1.

Example 3 describes the synthesis of tertiary amine ROMP polymer.

The results of Example 4 show that the synthesized ROMP resin can be used for the successful removal of ^{18}F -fluoride from aqueous media (such as that obtained from the cyclotron target). Furthermore the fluoride can be removed from the resin (in yields of up to 80 %) by flushing the resin with K_2CO_3 (aq). Lastly it has been shown that the performance of the ROMP resin is at least equivalent if not superior to what is arguably the industrial standard solid phase for this application.

Example 5 relates to the cartridge testing of ROMP fluoride extraction polymer for extraction of fluoride from target water.

Example 6 describes a process for the production of ^{18}F FDG on a microfabricated device.

Example 7 relates to the creation of a predetermined network of microchannels on the surface of a glass, silicon or polymer substrate.

Example 8 relates to coating the surfaces of a microfabricated device with ROMP polymer having tetraalkylammonium side chains.

Example 9 describes a process used for the recovery of ^{18}F fluoride from ^{18}O -enriched water using the device of the present invention.

Brief Description of the Figures

Figure 1 illustrates the reaction scheme used for synthesis of ROMP monomer for fluoride (ion-exchange) extraction.

Figure 2 shows the chemical structure of the synthesised cross-linker.

Figure 3 illustrates the reaction scheme used for synthesis of tertiary amine ROMP polymer.

Figure 4A illustrates the chemical structures of tertiary amine resin, quaternary-ammonium resin, and QMA resin.

Figure 4B illustrates the set up used for testing ROMP fluoride extraction polymer for extraction of fluoride from target water.

Figure 4C shows the extraction of ^{18}F -fluoride from aqueous media via the process of ion-exchange.

Figure 5 illustrates the set up for conducting cartridge testing of ROMP fluoride extraction polymer for extraction of fluoride from target water.

- 5 Figure 6A illustrates the radiofluoridation of the precursor of $[\text{}^{18}\text{F}]$ -FDG. Ac represents an acyl protecting group.

Figure 6B illustrates a sample radio-HPLC trace of the radiochemical composition of the collection vial contents obtained following radiofluoridation of the precursor of $[\text{}^{18}\text{F}]$ -FDG on a microfabricated device.

- 10 Figure 6C illustrates the change in behaviour of the resin over time (despite conditioning prior to each experiment) and a trend to ever less efficient fluoride extraction.

Figure 7 illustrates the steps involved in the creation of a predetermined network of microchannels on the surface of a glass, silicon or polymer substrate.

- 15 Figure 8 shows the synthesis of a ROMP polymer having a tetraalkylammonium side chain, wherein R^3 to R^5 are independently C_{1-6} alkyl groups.

Figure 9 is a schematic diagram showing how the polymerisation is carried out in the microchannels of a microfabricated device. The centre flow (white) is the gas (from a regulated cylinder) and the liquid flow (black) through the side indentations (from syringe pumps) is the ROMP polymer reaction mixture.

- 20 Figure 10 shows a schematic of a microfabricated device as well as micrographs at x25 and x100 of the microchannels coated with ROMP polymer.

Figure 11 illustrates retention of $[\text{}^{18}\text{F}]$ -fluoride on the polymer on a microfabricated device through ion exchange following introduction of an aqueous solution of $[\text{}^{18}\text{F}]$ fluoride. R^3 to R^5 are independently C_{1-6} alkyl groups.

- 25 **Example 1: Synthesis of ROMP monomer for fluoride (ion-exchange) extraction**

The reaction scheme is illustrated in Figure 1.

(a) Preparation of Acid Chloride

To 10g (72 mMol) of Norbornene carboxylic acid 1 was added 10.4 ml of Thionyl Chloride 2 (17g or 144mMol). The mixture was stirred under a nitrogen atmosphere for 2 hours (Reaction mixture is a clear Champaign coloured liquid).

- 5 Excess Thionyl chloride was then removed on a rotary evaporator by the addition of aliquots (4 x 6 ml) of toluene at approximately 45°C. The acid chloride 3 could be stored for up to a week before use providing it was kept refrigerated and under nitrogen.

(b) Reaction of Acid Chloride with Amine

- 10 To the acid chloride 3 was added 15 ml DCM and the mixture chilled on ice. 0.8 equivalents (5.92g, 58 mMol, 7.3 ml) of amine 4 were then added drop-wise with stirring. The reaction mixture was then allowed to reach RT and left to react for a further two hours. This entire procedure was performed under a nitrogen atmosphere (After amine addition reaction mixture appears as an opaque honey colour solution containing white precipitate).

15 (c) Purification of crude monomer mixture

- 20 After the two hours reaction time the reaction mixture was extracted with 3 x 10 ml of 30 % v/v conc. H₃PO₄ (pH ~2). The combined aqueous components were then adjusted to pH 12 using conc. NaOH(aq) and extracted with 4 x 12 ml DCM. The combined DCM fragments were dried over MgSO₄, filtered and the DCM removed under reduced pressure to yield the purified monomer 5 (11.2 g heavy golden oil, 87%).

Elemental C:H:N analysis gave 64.99% C, 9.34% H and 11.30% N. (expected values calculated from C₁₃H₂₂N₂O, formula weight = 222 were 70.23% C, 9.97% H and 12.60% N).

Example 2: Synthesis of cross-linker

- 25 Figure 2 shows the chemical structure of the synthesised cross-linker.

To a stirred solution of 1,4-Diiodo-benzene (9.90 g, 30 mMol), norbornadiene (35 ml, 325 mMol), piperidine (14.9 ml, 50 mMol) and (AcO)₂(PPh₃)₂Pd(II) (0.674 g, 3 mMol) in

DMF (45 ml) was added dropwise formic acid (3.46 ml, 63 mMol). A considerable amount of heat was evolved and the mixture went into solution. The reaction was followed using TLC (hexane mobile phase on silica, $R_f(\text{cross linker}) = 0.5$). Spots were elucidated using UV. After 41 hrs the reaction was quenched with water (200 ml) and the resulting mixture extracted with hexane (4 x 100 ml). The combined organic phase was washed with 10 % NaOH (3 x 100ml), 10 % H_3PO_4 (3 x 100 ml), water (3 x 100 ml) and saturated brine (1 x 100 ml). The organic phase was then dried over MgSO_4 and concentrated to give a dark red oil.

Purification was achieved in two stages via silica chromatography (hexane). A short primary column removed the dark red impurity ($R_f = 0-0.1$) to give a colourless oil. Further purification on a larger column yielded 3.64 g of a white solid **1** (46 %).

Mass spectrometry (EI +ve mode) of the product gave a peak at $m/z = 262$ $[\text{M}]^+$.

Elemental C:H analysis gave 91.51% C and 8.63% H (expected values calculated from $\text{C}_{20}\text{H}_{22}$, formula weight = 262 were 91.55% C, 8.45% H). $^1\text{H-NMR}$ in CDCl_3 , $\delta(\text{ppm})$ relative to tetramethylsilane (TMS): 7.2 (s, 4H, Aryl-CH), 6.2 (d m, 4H, Vinyl-CH), 2.95 (broad s, 2H, allylic-CH), 2.88 (broad s, 2H, allylic-CH), 2.7 (m, 2H, benzylic-CH).

Example 3: Synthesis of tertiary amine ROMP polymer

Figure 3 illustrates the reaction scheme used for synthesis of tertiary amine ROMP polymer.

To a 50 ml round bottom flask was added monomer **1** (2 g, 9 mMol), cross linker (0.262 g, 1 mMol), THF (12 ml) and DCM (2 ml). The contents of the flask were then mixed thoroughly and flushed with nitrogen. To this solution was added catalyst (0.09 g, ~1%) in DCM (1 ml) and again the contents mixed. The static reaction mixture was then left under an inert atmosphere at 40 °C for one hour.

After one hour the crude resin product (translucent brown gel) was broken into several fragments with a spatula and 20 ml of the following mixture was added: 75% THF, 20% CH_3CN and 5 % Ethyl Vinyl Ether. A condenser was then fitted and the mixture was refluxed at 120 °C under nitrogen for 1 hr. The resin was then transferred to a glass funnel with a frit and washed with sequential THF (20 ml) followed by diethyl ether (20 ml) a total of three times before being dried under vacuum. The dried resin product **3**

appears as a mottled brown solid (see figure A) (1.79 g, 79%, theoretical loading 3.98 mMol/g).

For production of the quaternary ammonium salt polymer 4, polymer 3 (1 g) was added to methyl iodide (10 equivalents, 39.8 mMol, 5.65g, 2.5 ml), THF (16 ml) and DCM (10 ml) and refluxed (85 °C) under a nitrogen atmosphere for 1 hr. The polymer was then transferred to a glass funnel with frit and washed with DCM (3 x 20 ml) and diethyl ether (3 x 20 ml) before being dried under vacuum (1.44 g, 92%).

Elemental C:H:N:I analysis gave: 50.64% C, 7.48% H, 5.77% N and 27.34% I (expected values calculated from a "theoretical" monomer unit of $C_{14.44}H_{24.78}N_{1.85}O_{0.93}I_{0.93}$, formula weight = 356.5 were: 48.66% C, 6.95% H, 7.22% N, and 32.95% I).

Example 4: Testing of ROMP fluoride extraction polymer for extraction of fluoride from target water

1.5 ml of aqueous ^{18}F -fluoride (i.e. mixture direct from target) measuring approximately 3 MBq (3 mCi) was loaded into a 2.5 ml plastic funnel (Mobitec column, see Figure 4B) containing 0.1 g resin and the mixture agitated for 40 minutes. A further three additional funnels containing silica, tertiary amine resin (1 Figure 4A) and solid phase removed from a Waters AccellTM QMA Sep-Pack (3 Figure 4A) were also loaded with aqueous ^{18}F -fluoride and treated analogously. These served as a control and two comparison groups respectively. After agitation the columns were purged of liquid and flushed with water (3 x 1ml). Both the radioactivity retained on the solid phase as well as that flushed from the funnel was measured.

A representative set of results is shown in the table below.

Solid phase	Activity retained on resin after water wash.	Activity retained on resin after wash with 1M K_2CO_3 (aq)
Tertiary amine <u>1</u>	45 %	-
quaternary-ammonium resin <u>2</u>	91 %	22 %
QMA resin <u>3</u>	94 %	5 %
Silica	7 %	-

Though the above results established resin function, direct comparisons of extraction efficiency between resins 2 and 3 (Figure 4A) were approximate due to the difference in

respective counter ions (iodide & chloride respectively). To remedy this, the experiment was repeated with the QMA and quaternary ammonium resins after they were each conditioned with 1M K_2CO_3 (3 x 1ml) and water (3 x 1 ml). This meant that both resins were in the carbonate form where by a direct comparison could be made. The table below shows a set of representative results.

Solid phase	Activity retained on resin after water wash.	Activity retained on resin after wash with 1M K_2CO_3 (aq.)
quaternary-ammonium carbonate resin	39 %	24 %
QMA carbonate resin	14 %	28 %

Extraction of ^{18}F -fluoride from aqueous media is achieved via the process of ion-exchange as shown in Figure 4C.

Example 5: Cartridge testing of ROMP fluoride extraction polymer for extraction of fluoride from target water

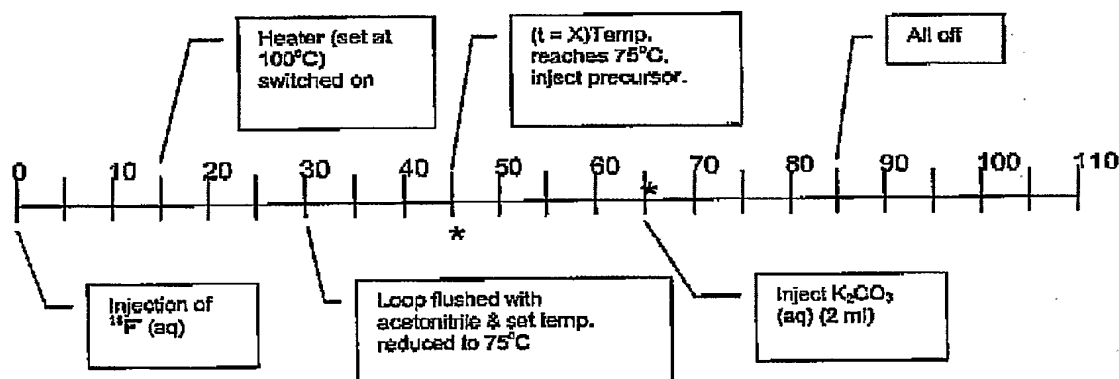
- 10 The set up for conducting this experiment is illustrated in Figure 5. The set up consists of a HPLC pump (2) that supplies a continuous flow of acetonitrile (1) through a HPLC injection valve (3) and onto the column containing the resin (5). Reagents including: water, K_2CO_3 (aq) and aqueous ^{18}F -fluoride are contacted with the resin by loading onto a 2 ml stainless steel loop before being injected (as a liquid plug) into the acetonitrile stream by switching the valve. Liquid output from the column and waste from the loop are collected in containers (10) and (4) respectively. The column can be heated to a preset temperature using a heating system, made up of a moulded aluminium block (6), a thermocouple (8), a band heater (7) and a temperature controller (9). The resin is kept within the column (5) using PTFE frits (filter discs) at both the column input and column output.

25 The basic fluoride extraction/recovery experiment conducted on the column proceeded as follows. Dry ammonium resin (chloride salt) (0.15 g) was loaded onto the column and the system assembled. The HPLC pump was then set to administer a continuous flow of acetonitrile at a flow rate of 0.5 ml/min. At this flow rate the resin was conditioned with plugs of K_2CO_3 0.5 M (3 x 2 ml) and water (3 x 2 ml) each injected via the loop/HPLC valve. The acetonitrile flow was then reduced to 0.2 ml/min and ^{18}F -fluoride approximately 370 MBq (10 mCi) made up to 1 ml with water was injected onto the

column. After 15 min the flow was increased to 0.5 ml/min for a further 5 minutes after which the Radioactivity in the collection vial (10) was measured. The percentage activity that passed through the column without being extracted was consistently <1 %. Next the output vial (10) was refreshed and the resin flushed with 2 ml of K_2CO_3 0.5M at 0.5 ml/min. This step exchanged the fluoride immobilized on the resin with carbonate causing the radioactivity to leave the column and be recovered in the collection vial. Using this method it was possible to retain fluoride on the resin and then subsequently recover it into 0.5 M K_2CO_3 (2 ml) at efficiencies averaging 98 %.

Example 6: Production of [^{18}F]FDG on a microfabricated device

The method for extracting the fluoride onto the resin was achieved as detailed in Example 5. Having injected the aqueous fluoride onto the column ($t = 0$ min) at 0.2 ml/min over a period of 15 min, the column was heated to 100 °C, for a further 15 minutes while maintaining the flow of acetonitrile. This procedure was designed to azeotropically remove all water from the column. Then at $t = 30$ min the loop was flushed with anhydrous acetonitrile and the set temperature reduced to 75 °C. On attainment of the set temperature ($t = X$ min) a solution of **1** (20 mg in 1 ml CH_3CN ; Figure 6A) was loaded onto the loop and injected onto the column. Lastly at $t = X+20$ the column was flushed with K_2CO_3 (aq) 0.5 M (2M). This procedure is summarized in the *time-line* shown below.



The horizontal scale is in minutes, along which are marked the various operations. The "*" marks denote points when the column output vial was refreshed. Note also that the entire process is conducted with a continuous flow of acetonitrile (0.2 ml/min).

Less than 2 % of the overall radioactivity eluted from the column (/resin) prior to introduction of the K_2CO_3 (aq). With the introduction of K_2CO_3 (aq) onto the resin the radioactivity was almost quantitatively eluted into the collection vial (ca 99 %). The radiochemical composition of the collection vial contents was then determined using
5 radio-HPLC. See sample trace in Figure 6B.

Over the course of 4 experiments using the same resin sample a greater percentage of the activity was seen to elute from the column prior to the base flush. By the 4th experiment this percentage had grown to approximately half the total activity. This
10 ~~change in behaviour was associated with a discolouration of the resin~~ (despite conditioning prior to each experiment) and a trend to ever less efficient fluoride extraction (see Figure 6C).

Example 7: Creation of a predetermined network of microchannels on the surface of a glass, silicon or polymer substrate

Figure 7 illustrates the steps involved in the creation of a predetermined network of
15 microchannels on the surface of a glass, silicon or polymer substrate.

Masks made using a direct write lithography system were used to shadow cast (expose) substrates. After shadow casting, the exposed area of photoresist and subsequently chromium were selectively removed. Next etching using an aqueous solution 5 % (7:1 $NH_4F:HF$), 9.25 % HCL were used to create open channels (etch rates of $0.2 \mu m min^{-1}$)
20 OF 50 μm depth. Following etching, both resist and chromium layers were removed. To complete the process a pre-drilled cover plate (microscope slide) and etched substrate were sonicated in DMF, acetone and methanol (2 min each) and immersed in conc. sulphuric acid (2hrs). Further washing with ultra pure water and drying under a flow of nitrogen, preceded loading of the furnace. Thermal bonding used a 12 hr ramped
25 temperature programme with a maximum temperature of 600°C.

76 mm Low Reflective Chrome (Cr 1000@), print grade sensitised, Soda Lime glass substrates of thickness 0.01" and 0.06" were purchased from Nanofilm (Westlake Village, Canada). Clear Soda-lime glass microscope slide 26 mm x 75 mm x 1 mm, hydrochloric acid (HCl), acetone, methanol, ammonium fluoride solution (NH_4F),
30 hydrofluoric acid (HF) and sulphuric acid (H_2SO_4 sp.gr. 1.84) were purchased from

BDH. Dimethylformamide (DMF) was purchased from Aldrich. Shipley's Microposit 351 developer and Shipley's chrome etchant 18 were purchased through Chestech Ltd. (Chestech Ltd., Rugby, Warwickshire, UK). Teflon tubing 1.6 mm (1/16") o.d. 380 μ m i.d. was supplied by Upchurch Scientific. GlasSeal Connectors, 1.6 mm (1/16") steel unions, peek fingertight fittings and fused silica capillary (375 μ m o.d.) were supplied by Supelco. Araldite 2014 epoxy was supplied by RS-Components.

Chip design was done on a PC running AutoCad LT for Windows 95. The Direct Write Laser system was a prototype DWLII system from Heidelberg Instruments (Heidelberg Instruments Mikrotechnik GmbH, 69126 Heidelberg, Germany). Furnace used for glass bonding were Thermicon P (Heraeus) instruments.

Example 8: Coating the surfaces of a microfabricated device with ROMP polymer having tetraalkylammonium side chains

A solution of the monomer Compound 1 (Figure 8), crosslinker and catalyst in tetrahydrofuran was introduced into the device, which was heated using a chromium electrode and an applied voltage of 120 V ($\sim 80^{\circ}\text{C}$) to allow polymerisation to occur on the internal surfaces of the device. At the same time a stream of nitrogen was flowed through the microchannels such that the polymer did not block the microchannels (Figure 9). The nitrogen supply was at 1.5 Bar (1-2ml/min approx) and the liquid flow was 5-10 μ l/min. The width of the microchannel (not that defined by the gas flow) was 150 μ m.

Figure 10 shows a schematic of a microfabricated device as well as micrographs at x25 and x100 of the microchannels coated with ROMP polymer.

The trialkylammonium group on the polymer (compound 2) was then converted to a tetraalkylammonium group (compound 3) *in situ* by methylation as shown in Figure 8.

Example 9: Recovery of [^{18}F]fluoride from ^{18}O -enriched water

Into the device prepared according to Example 8 was introduced an aqueous solution of [^{18}F]fluoride. As this passed through the microchannels the [^{18}F]fluoride was retained on the polymer through ion exchange (as illustrated in Figure 11) and enriched water was recovered from the exit port of the device.

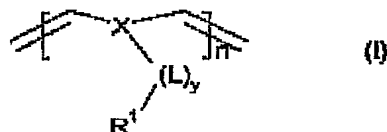
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The polymer can be dried by passing
microchannels with heating.

anhydrous acetonitrile through the

Claims

- 1) A device adapted to carry out a solid-phase radiochemical process characterised in that the solid-phase radiochemical process is carried out on the internal surfaces of said device wherein said internal surfaces are coated with a Ring Opening Metathesis Polymerisation (ROMP) polymer.
- 2) The device of claim 1 wherein the ROMP polymer is of Formula I:



wherein:

X is either a C₁₋₆ hydrocarbon chain or a C₄₋₆ alicyclic group;

R¹ is selected from hydrogen, hydroxyl, halogen, nitro, cyano, -SH, -N=C=O, C₁₋₂₀ alkyl, C₄₋₁₂ aryl, C₃₋₂₀ alkylaryl, C₂₋₂₀ acyl, C₂₋₂₀ functionalised acyl, C₁₋₂₀ formyl, C₁₋₂₀ functionalised formyl, C₁₋₂₀ alkoxy, C₁₋₂₀ functionalised alkoxy, C₁₋₂₀ amino, C₁₋₂₀ functionalised amino, C₃₋₁₈ trialkylammonium, C₃₋₁₈ trialkylammonium with bound fluoride ion, C₁₋₂₀ imino, C₁₋₂₀ functionalised imino, C₁₋₂₀ amido, C₁₋₂₀ functionalised amido, C₁₋₂₀ nitroalkyl, C₁₋₂₀ functionalised nitroalkyl, C₁₋₂₀ carboxyl, C₁₋₂₀ functionalised carboxyl, carbonate, C₂₋₂₀ carboalkoxy or C₂₋₂₀ functionalised carboalkoxy or R¹ optionally further comprises a radiotracer precursor, a catalyst or an enzyme;

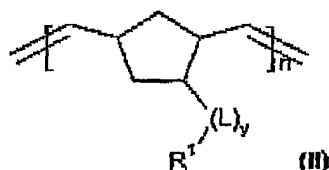
-(L)_x is linker group wherein each L is independently -CY₂-, -CY=CY-, -C≡C-, -CY₂CO₂-, -CO₂CY₂-, -NYCO-, -CONY-, -NY(C=O)NY-, -NY(C=S)NY-, -SO₂NY-, -NYSO₂-, -CY₂OCY₂-, -CY₂SCY₂-, -CY₂NYCY₂-, a C₄₋₈ cycloheteroalkylene group, a C₄₋₈ cycloalkylene group, a C₅₋₁₂ arylene group, or a C₃₋₁₂ heteroarylene group, or an amino acid, wherein Y is independently chosen from H, C₁₋₄ alkyl, C₂₋₄ alkenyl, C₂₋₄ alkynyl, C₁₋₄ alkoxyalkyl or C₁₋₄ hydroxyalkyl and y is an integer of value 0 to 10; L is optionally further substituted with one or more R² groups where R² is selected from hydrogen, hydroxyl, halogen, nitro, cyano, -SH, -

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N=C=O, C₁₋₂₀ alkyl, C₄₋₁₂ aryl, C₃₋₂₀ alkylaryl, C₂₋₂₀ acyl, C₂₋₂₀ functionalised acyl, C₁₋₂₀ formyl, C₁₋₂₀ functionalised formyl, C₁₋₂₀ alkoxy, C₁₋₂₀ functionalised alkoxy, C₁₋₂₀ amino, C₁₋₂₀ functionalised amino, C₃₋₁₈ trialkylammonium, C₁₋₂₀ imino, C₁₋₂₀ functionalised imino, C₁₋₂₀ amido, C₁₋₂₀ functionalised amido, C₁₋₂₀ nitroalkyl, C₁₋₂₀ functionalised nitroalkyl, C₁₋₂₀ carboxyl, C₁₋₂₀ functionalised carboxyl, carbonate, C₂₋₂₀ carboalkoxy or C₂₋₂₀ functionalised carboalkoxy; and,

n = number of polymer units.

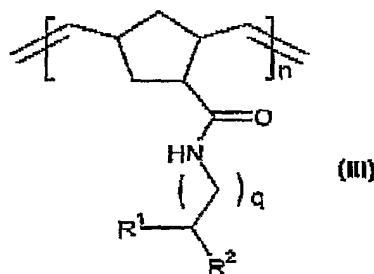
3) The device of claim 1 wherein the ROMP polymer is of Formula II:



10 wherein:

-(L)_y, R¹ and n are as defined in claim 2 for Formula I.

4) The device of claim 1 wherein the ROMP polymer is of Formula III:



wherein:

15 R¹ and n are as defined in claim 2 for Formula I;

R² is an optional group as defined in claim 2 for -(L)_y of Formula I; and,

q = 1-4.

5) The device of any of claims 1-4 wherein R^1 is a group suitable for binding an ^{18}F -fluoride ion.

6) The device of claim 5 wherein R is a trialkylammonium group of Formula IV:



5 wherein R^{3-5} are each independently a C_{1-6} alkyl group.

7) The device of either of claims 5 or 6 further comprising a bound ^{18}F -fluoride ion.

8) The device of any of claims 1-4 wherein R^1 is a C_{1-20} alkyl group.

9) The device of any of claims 1-4 wherein R^1 is $-\text{N}=\text{C}=\text{O}$.

10) The device of any of claims 1-4 wherein R is a group comprising an enzyme.

10 11) The device of any of claims 1-4 wherein R^1 is $-\text{SH}$.

12) The device of any of claims 1-11 which is a microfabricated device.

13) A method for the production of the device of claim 12 comprising:

(i) creating a defined network of microchannels within said device;

(ii) heating the device to a temperature of between 80°C and 140°C ; and,

15 (iii) passing a solution of monomer, crosslinker and catalyst through the microchannels while concurrently introducing a flow of nitrogen through the microchannels such that ROMP polymer is deposited on walls and indentations of the microchannels.

14) The method of claim 13 wherein step (i) comprises:

20 (a) providing a suitable substrate;

(b) marking a specific pattern onto the surface of said substrate;

(c) etching the pattern into the surface of said substrate; and

(d) attaching a cover to the etched surface of step (c) thereby forming channels.

15)The method of claim 13 wherein step (i) comprises the use of a polymer in a process selected from injection moulding, hot embossing, casting, lithography or machining.

16)An automated synthesis system comprising a series of interconnected devices
5 wherein each device is a device according to claims 1-12 wherein said devices are:

- (i) a mixing and reaction device;
- (ii) an analysis device; and,
- (iii) a separation device.

17)Use of the device of any of claims 1 to 12 for:

- 10
- (i) recovery of radioisotopes;
 - (ii) radiochemical synthesis; or
 - (iii) radiochemical purification.

18)The use of claim 17 wherein said recovery of radioisotopes is recovery of ^{18}F -fluoride ion from ^{18}O -enriched water containing ^{18}F -fluoride ion or natural water
15 containing ^{18}F -fluoride ion.

19)The use of claim 18 wherein said device is a device according to either of claims 5 or 6.

20)The use of either of claims 18 or 19 wherein the recovered ^{18}F -fluoride ion is used for a radiofluoridation reaction *in situ* or is recovered in a suitable solvent.

20 21)The use of claim 17 wherein said radiochemical synthesis is an enzymatic chemical reaction.

22)The use of claim 17 wherein said radiochemical synthesis is a radiofluoridation.

23)The use of claim 22 wherein the radiofluoridation forms a step in the production of an ^{18}F -labelled radiotracer.

24)The use of claim 23 wherein said ^{18}F - labelled radiotracer is ^{18}F -FDG, ^{18}F -FDDNP, ^{18}F -F-DOPA or ^{18}F -FLT.

25)The use of any of claims 22 to 24 wherein said device is a device according to claim 7.

5 26)The use of claim 17 wherein said radiochemical purification comprises chromatographic separation.

27)The use of claim 17 wherein said radiochemical purification is removal of secondary amine, hydroxyl or thiol from alkylation reactions wherein the alkylated product is radiolabelled.

10 28)A process for labelling the precursor of a radiotracer with a radiolabel characterised in that the radiolabel is provided bound to a ROMP polymer.

29)A process for labelling the precursor of a radiotracer with a radiolabel characterised in that the precursor is provided bound to a ROMP polymer.

30)The process of either of claims 28 or 29 wherein said radiotracer is ^{18}F , ^{11}C , $^{99\text{m}}\text{Tc}$.

Abstract

The present invention involves the application of ROMP polymers to the internal surfaces of a device for the purpose of carrying out a solid-phase radiochemical process within the device. An additional embodiment of the invention is an automated synthesis
5 system comprising a number of devices of the invention in order that a series of processes can be carried out in direct sequence. In a preferred embodiment, the present invention is a microfabricated device.



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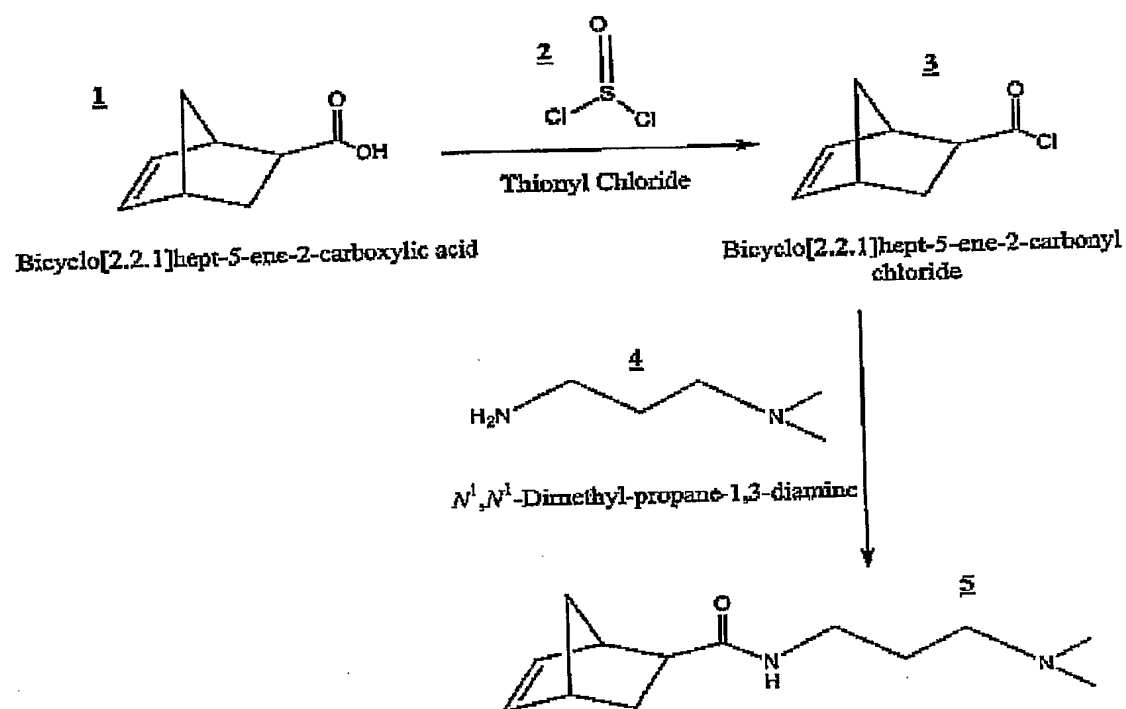
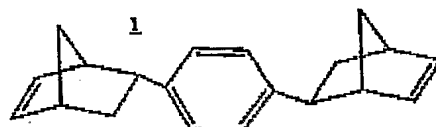
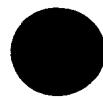


Figure 1



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**Figure 2**



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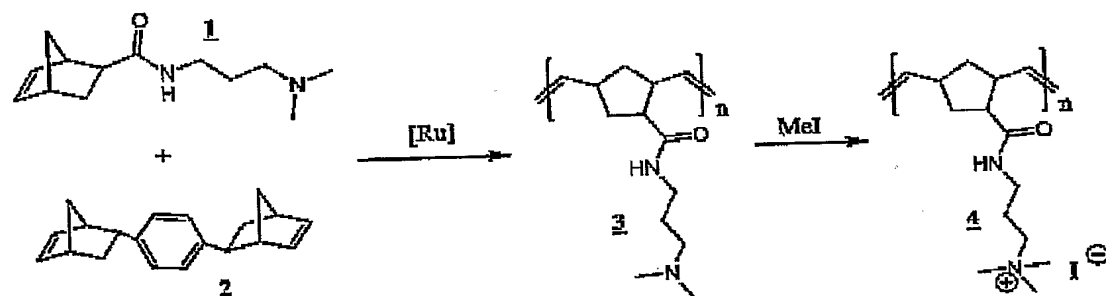


Figure 3



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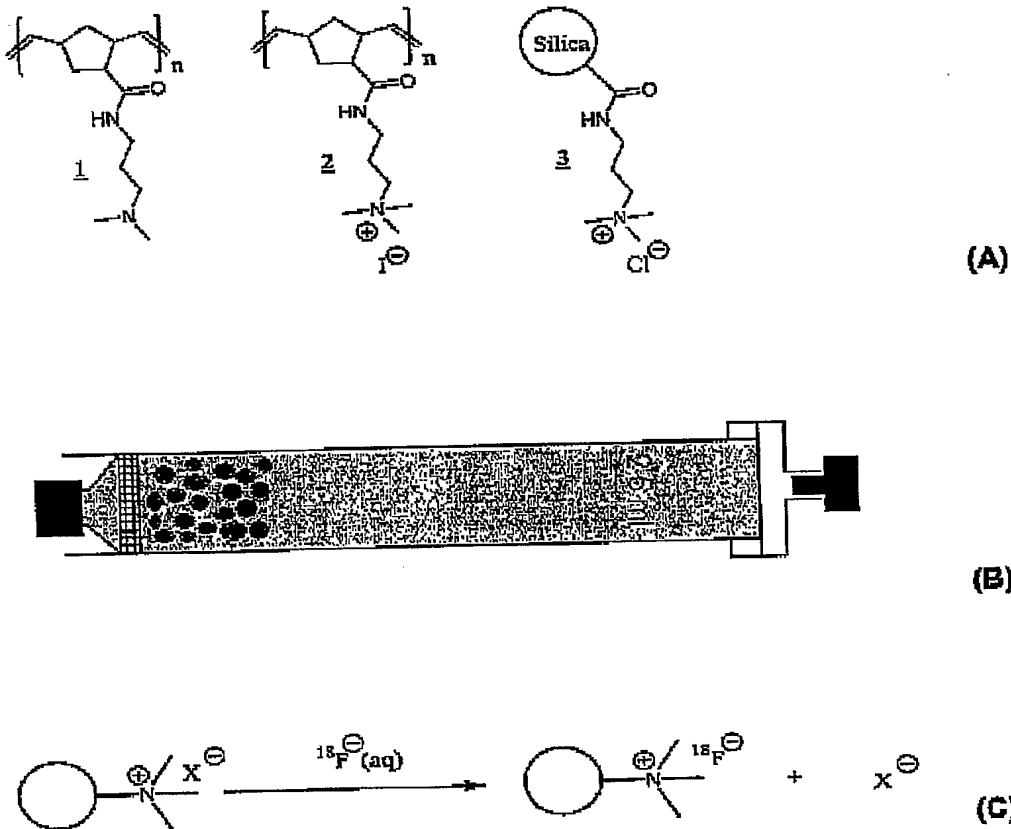


Figure 4



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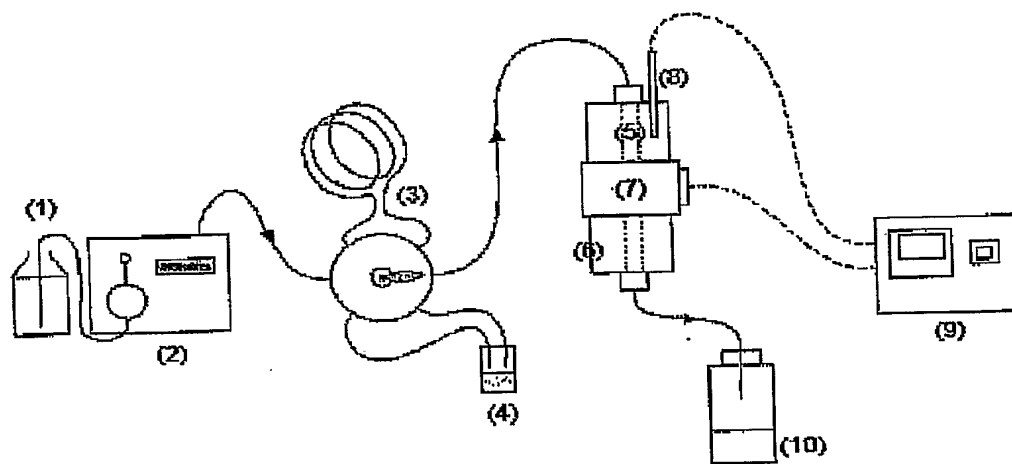
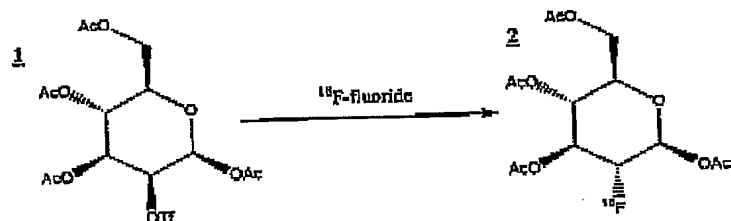


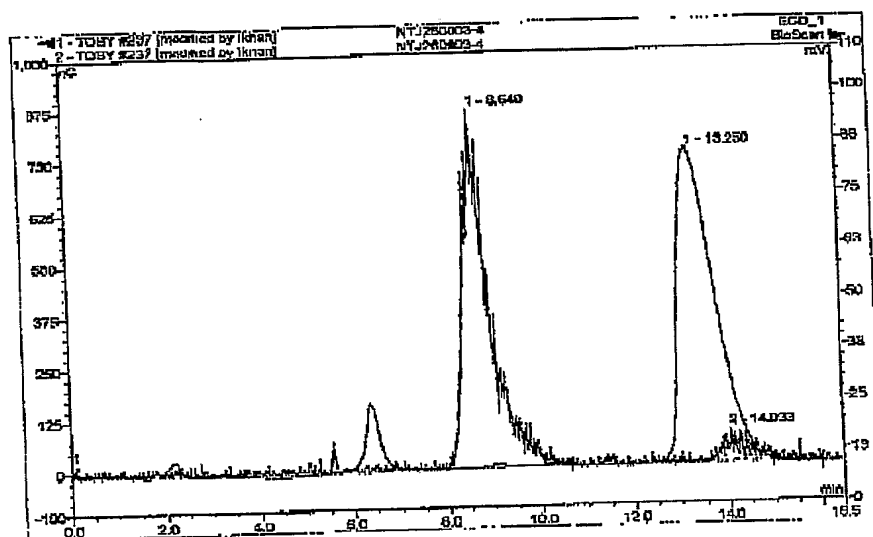
Figure 5



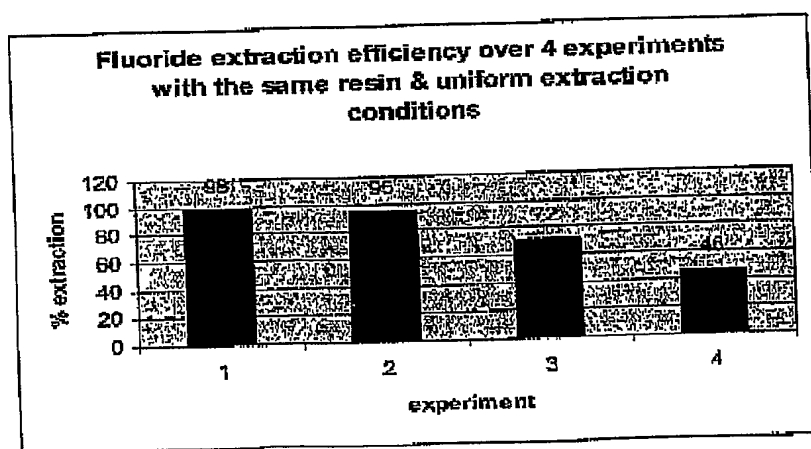
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(A)



(B)

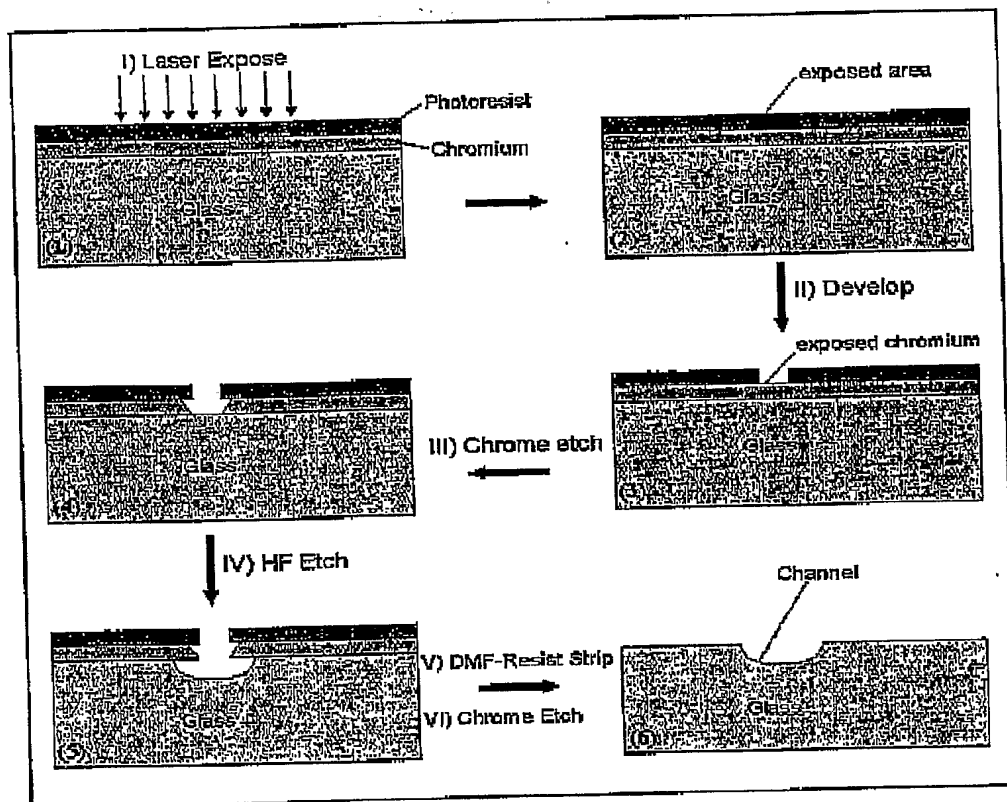


(C)

Figure 6



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**Figure 7**



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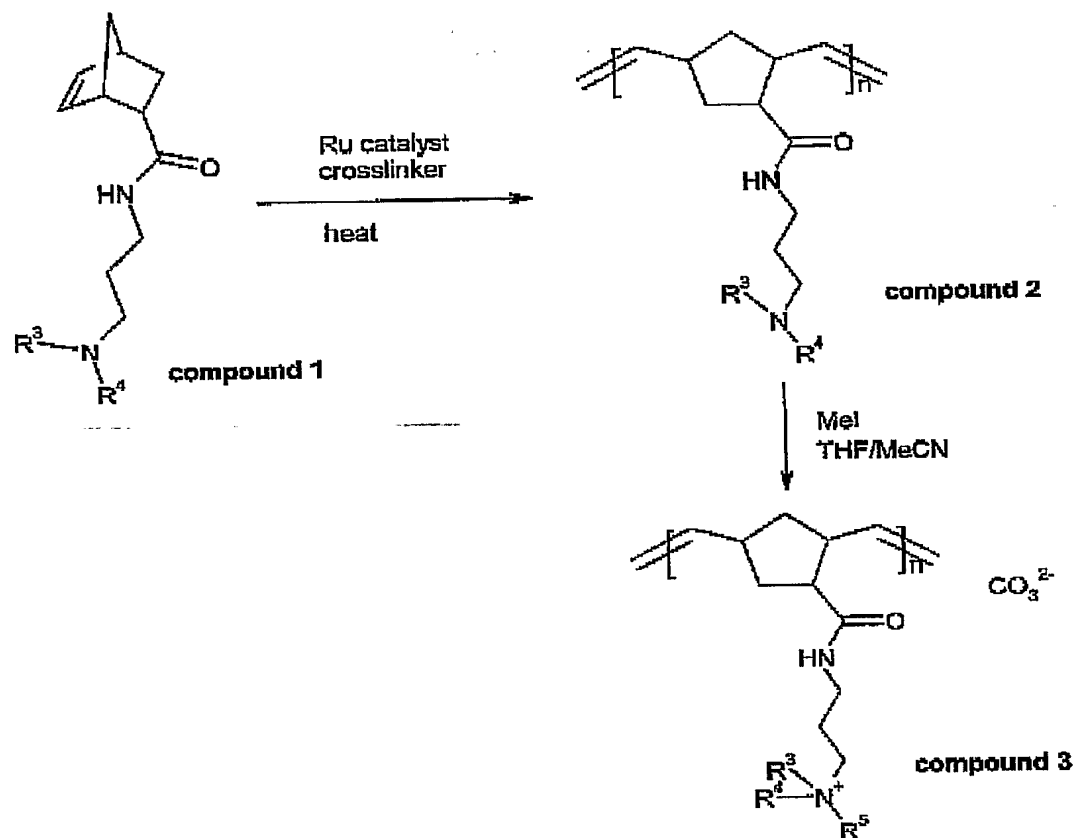


Figure 8



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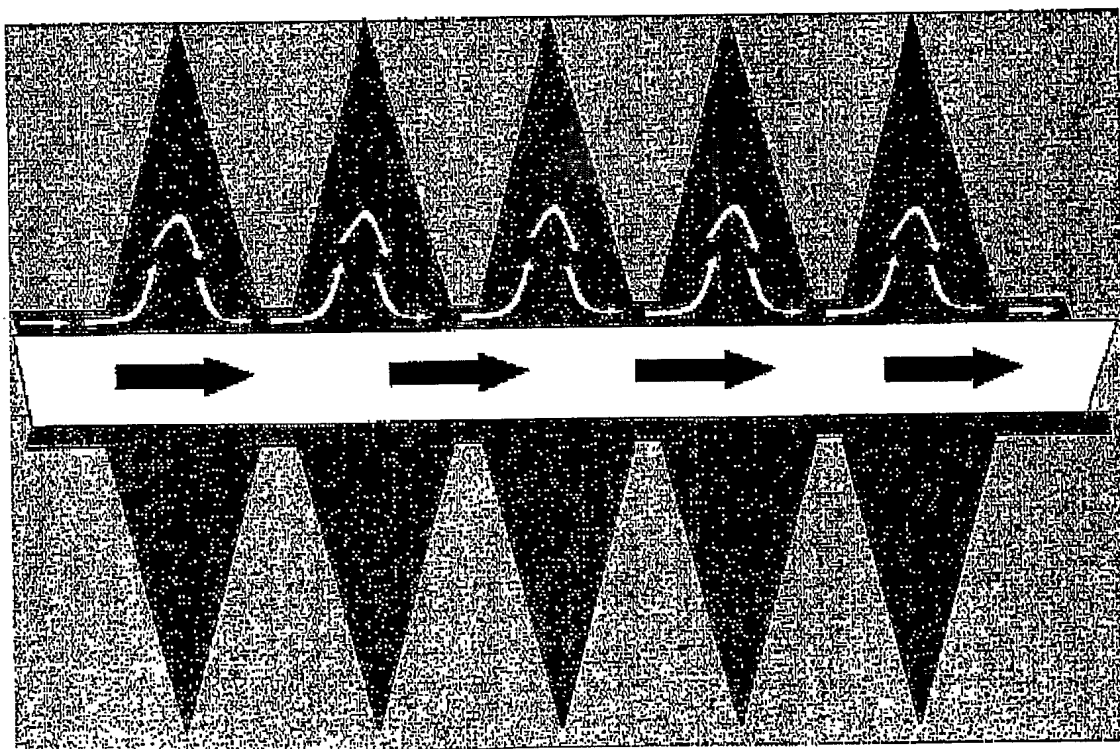


Figure 9



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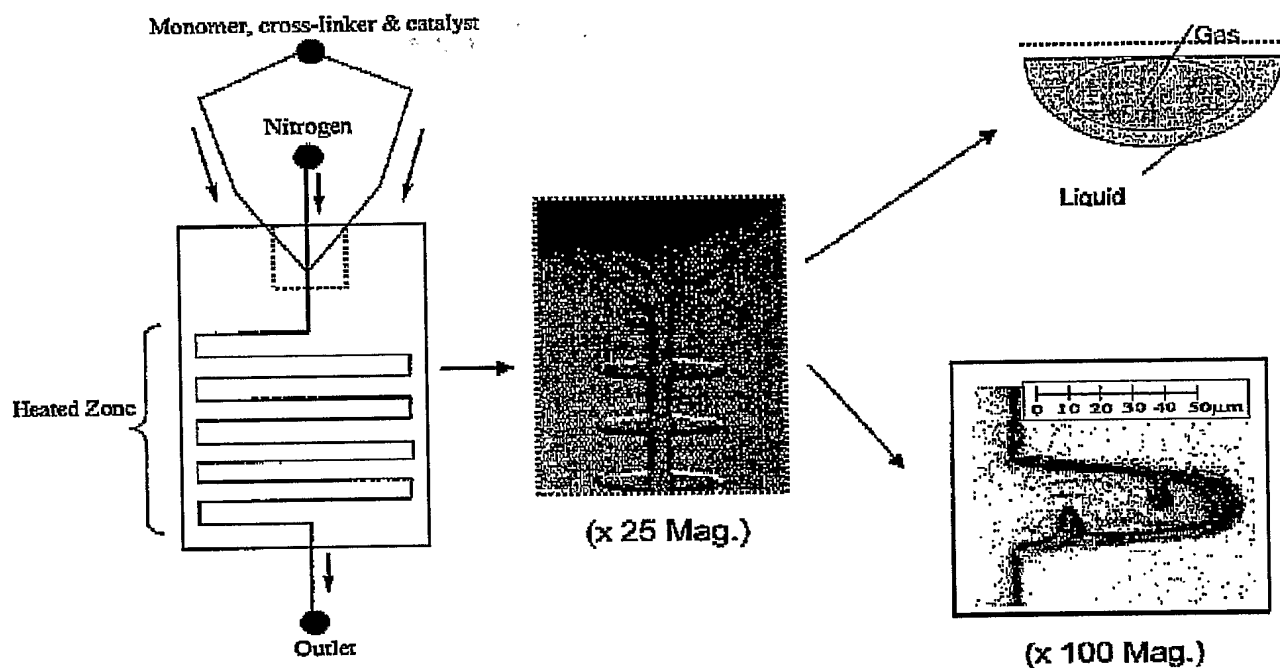


Figure 10



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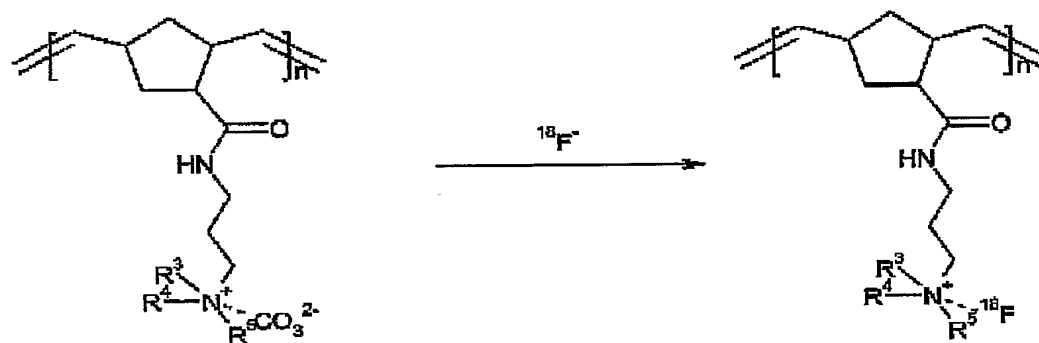


Figure 11

